MEMORANDUM

TO: The file
FROM: Anne M. Pilaro, Ph.D., Clinical Pharmacology/Toxicology Branch, DCTDA
THROUGH: M. David Green, Ph.D., Chief, Clinical Pharmacology/Toxicology Branch, DCTDA
STN BLA #: 103628\5021
SPONSOR: BIOGEN, INC.
PRODUCT: recombinant, human interferon-β 1a (AVONEX®, Chinese hamster ovary cell-derived), for the treatment of relapsing-remitting multiple sclerosis
AMENDMENT TYPE: change in formulation

DATE: August 26, 2002

SYNOPSIS:

The sponsor has submitted a supplemental Biologics Licensing application for a change in formulation of their currently marketed interferon-beta 1a product, AVONEX®. In this application, they are changing from the present, lyophilized formulation of interferon-beta 1a at 30 μg/ml in sodium phosphate buffered saline containing 1.5% human serum albumin, to a serum albumin-free formulation in sodium acetate buffer and 0.05% polysorbate 20 (Tween-20). The new material is to be provided in single-use, glass syringes with rubber tip caps, or with a [redacted] in place of the tip cap.

Analysis of the final, formulated product by [redacted] identified two [redacted] as contaminants of the interferon-beta 1a preparation (Section 1.5.4.8, *Impurities*, of the CMC section of the sBLA). These contaminants were only identified in interferon preparations stored in glass syringes with the rubber tip caps, and not in those with [redacted] On further analysis, these [redacted] were identified as containing [redacted] and [redacted] in the [redacted], and [redacted] and [redacted] in the [redacted] The approximate patient doses of each of these contaminants, as calculated by the sponsor, are [redacted] The schedule for dosing of multiple sclerosis patients with AVONEX® is weekly, for the life of the subject.

The sponsor states that the levels of each of these contaminants in the final, formulated drug product "...are approximately a million times lower than the corresponding LD_{50} limits for these compounds, based on animal toxicity data..." and that "As a result, they do not pose any safety concern in humans." The information cited by the sponsor from the Material Safety Data Sheets (MSDS) for each of the three contaminants has evaluated the acute toxicity of each agent following oral administration in rats and mice. The data for each of the compounds is presented in the Table, below:

[redacted]

Comment: None of these agents was tested for toxicity by the clinical route of administration for AVONEX®, which is intra-muscular (i/m).

Additional search of the literature and review of the existing toxicity databases has revealed that all three of these contaminants are highly lipid soluble, and the potential for accumulation and storage in fatty tissue following repeated exposure exists. All three compounds are listed on the Environmental Protection Agency's Toxic Substances Control Act as potential carcinogenic, tumorigenic, or tumor-promoting agents. However, genotoxicity data derived from the MSDS are either equivocal or non-existent, and other effects, including effects on reproductive accessory organs, nerve conduction velocity, liver and cardiac toxicities, effects on spermatogenesis, and tumors in F_1 or F_2 offspring were also reported. Therefore, a calculation of acceptable daily exposure limits for each of the three agents was performed, according to the procedures for setting exposure limits for residual, Class 2 solvents in pharmaceutical agents, and as described in the ICH Guidance Q3C, "Impurities: Guidelines for Residual Solvents." Data for the NOAEL of each compound in chronic exposure testing were derived either from published studies in the open literature, or from the International ARC monographs, where available.

A. ———————————————

——————— was not mutagenic when tested in the Ames assay, and inconclusive results were obtained in the mouse micronucleus assay. Carcinogenicity data for — after oral feeding were equivocal. Multiple studies in rats demonstrated no significant differences in incidence or type of tumors after feeding up to 1% — in food daily for two years, as compared to control animals. Studies in mice, however, demonstrated statistically significant increases in lung tumors over control groups after feeding 0.6% — in food daily for two years in $B6C3F_1$ mice, but no difference in tumor incidence or type between BALB/c mice fed control or 0.75% — for two years. A repeat of the carcinogenicity study in $B6C3F_1$ mice at a maximal dose of 0.5% — in feed for 96 weeks had no statistically significant differences in tumor incidence or type from the control group. These data were used to calculate an acceptable permitted daily exposure (PDE limit) for — in the proposed dose and schedule of AVONEX®, assuming that the bioavailability of the agent by both oral administration (the route tested in the carcinogenicity studies) and i/m injection (the clinical route of administration) were approximately the same.

Rats, NOAEL for carcinogenicity, 1% daily in feed x 2 years; estimated daily intake 0.1 g/d (in 10 gm food) for a 400 g rat is approximately 250 mg/kg/d

$$\frac{250\ \text{mg/kg/d} \times 60\ \text{kg (female human)}}{5 \times 10 \times 1 \times 1 \times 1} = \frac{1500\ \text{mg/d}}{500} = \textbf{3 mg/d(ose)}$$

Rat, NOAEL for reproductive toxicity, 25 mg/kg/d, p/o x 13 weeks

$$\frac{25\ \text{mg/kg/d} \times 60\ \text{kg (female human)}}{5 \times 10 \times 1 \times 10 \times 1} = \frac{1500\ \text{mg/d}}{500} = \textbf{3 mg/d(ose)}$$

Mouse, NOAEL for carcinogenicity, 0.5% daily in feed x 2 years; estimated daily intake 0.025 g/d (in 5 g food) for a 30 g mouse is approximately 0.83 mg/kg/d

$$\frac{0.83\ \text{mg/kg/d} \times 60\ \text{kg human}}{12 \times 10 \times 1 \times 1 \times 1} = \frac{49.8\ \text{mg/d}}{120} = \textbf{0.415 mg/d(ose)}$$

Dog, NOAEL for toxicity, tumorigenicity 24,411 mg/kg total estimated intake, 260 days

$$\frac{24111 \text{ mg/kg} \times 60 \text{ kg}}{2 \times 10 \times 10 \times 1 \times 1} = \frac{1446660}{200} \text{ (divided by 260 days)} = \textbf{27.8 mg/d(ose)}$$

tentative safety factor:
calculated acceptable daily exposure limit for [redacted] / estimated level of [redacted] in patient dose of AVONEX® = 0.415 mg/dose / 500 ng/dose = **830**

B. [redacted]

No carcinogenicity or mutagenicity data were available for this product. However, the toxicities of this product include anti-estrogenic effects, which were predominantly observed in male rats exposed to 80 mg [redacted] t.i.w. by s/c injection for 13 weeks. These data were used to calculate an acceptable PDE for [redacted] in the proposed dose and schedule of AVONEX®, assuming that the bioavailability of the agent by both s/c administration (the route tested in the male fertility and toxicity studies) and i/m injection (the clinical route of administration) were approximately the same.

Rat, NOAEL for effects on male reproductive accessory organs, spermatogenesis, 20 mg/rat t.i.w x 13 weeks (estimated 50 mg/kg for 400 gm rat)

$$\frac{50 \text{ mg/kg/dose} \times 60 \text{ kg}}{5 \times 10 \times 5 \times 10 \times 1} = \frac{3000 \text{ mg/dose}}{2500} = \textbf{1.2 mg/dose}$$

tentative safety factor:
calculated acceptable daily exposure limit for [redacted] / estimated level of [redacted] in patient dose of AVONEX® = 1.25 mg/dose / 60 ng/dose = **20,000**

C. [redacted]

No carcinogenicity or mutagenicity data were available for this product. Short-term toxicity studies in rats demonstrated a dose-related, reversible neurotoxicity as manifested by decreased conduction velocity in peripheral nerves, and increases in both absolute and relative refractory periods to further stimulation, in the absence of any microscopic evidence of nerve damage. In oral dosing studies in rats, the liver was identified as the target organ, and focal myocarditis was observed in male animals at doses of 150 mg/kg/d and higher. Female rats tended to demonstrate the peripheral neurotoxicities at lower doses than the male rats. Teratogenicity was not observed in two studies in rats, both of which included doses that were maternally toxic. These data were used to calculate an acceptable PDE for [redacted] in the proposed dose and schedule of AVONEX®, assuming that the bioavailability of the agent by both oral administration (the route tested in the neurotoxicity studies) and i/m injection (the clinical route of administration) were approximately the same.

Rat, NOAEL in female rats for effects on nerve conduction velocity, refractory time, 1.6 mg/kg/d x 14 d

$$\frac{1.6\ \text{mg/kg/dose X 60 kg}}{5 \times 10 \times 10 \times 10 \times 1} = \frac{96\ \text{mg/dose}}{5000} = \textbf{19.2 µg/dose}$$

Rat, NOAEL in male/female rats for liver toxicity, myocarditis, 15 mg/kg/d x 18 weeks

$$\frac{1.5\ \text{mg/kg/dose x 60 kg}}{5 \times 10 \times 5 \times 5 \times 1} = \frac{90\ \text{µg/dose}}{1250} = \textbf{72 µg/dose}$$

tentative safety factor:

calculated acceptable daily exposure limit for ——— / estimated level of —— in patient dose of AVONEX® $= \frac{19.2\ \text{µg/dose}}{20\ \text{µg/dose}} = 1$